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# Insulin-like Growth Factor 1 Effects on Epilepsy

*Corrin A. Pimentel, Dr. Yevgeny Berdichevsky*

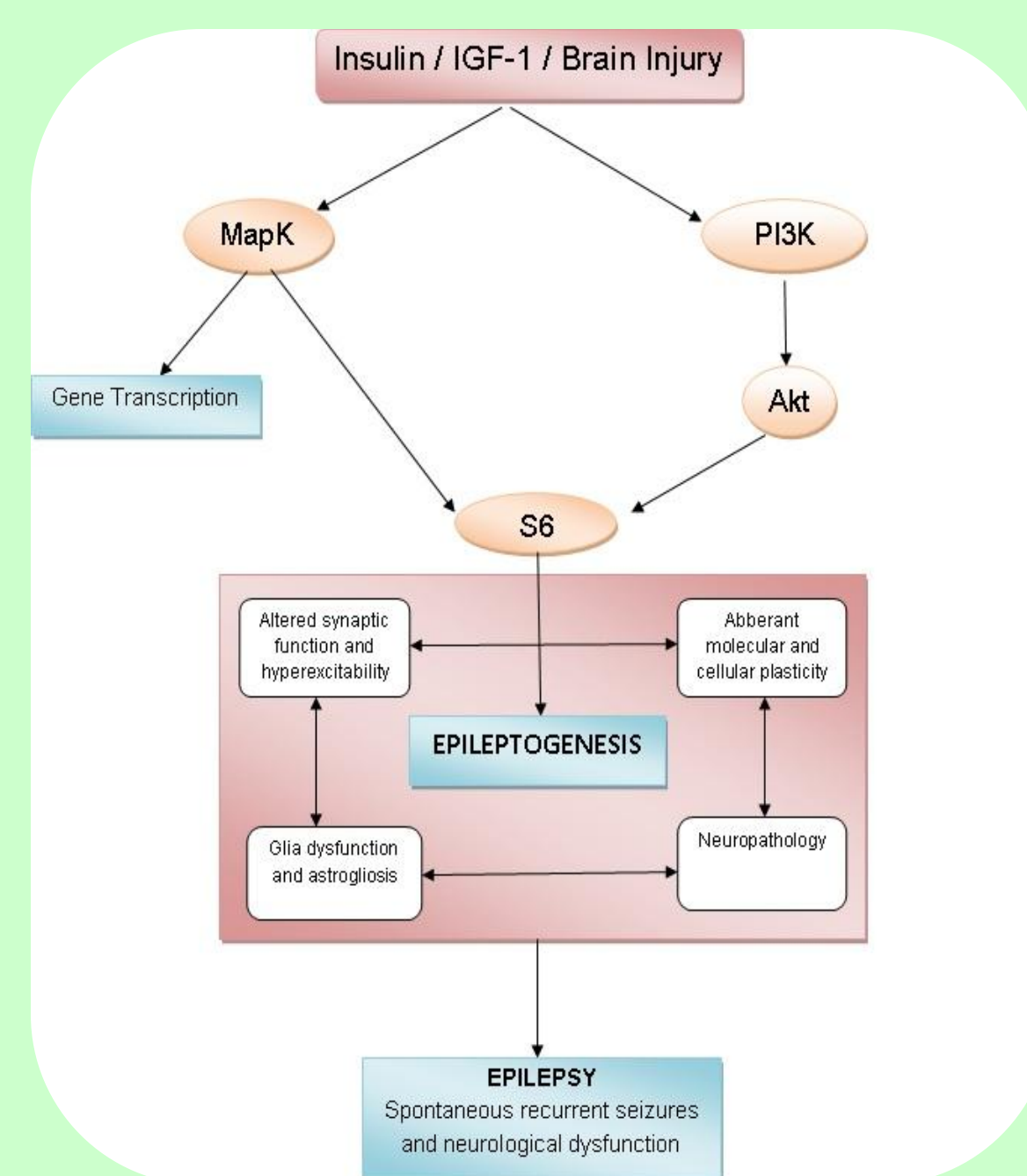
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## Significance

- According to the Center for Disease Control and Prevention, epilepsy affects 2.2 million Americans and 65 million people worldwide
- Epileptic seizures can severely limit school achievements, employment prospects, and participation in other life experiences.
- Traumatic brain injury is one of the major risk factors causing epileptogenesis; the development of epilepsy.

## Background Information

- Insulin-like growth factor 1 (IGF-1) levels are elevated in the brain following head injury
- Earlier research suggests that IGF-1 has pro-epileptogenic effects
- It is known that the binding of IGF-1 to IGF-1 receptors leads to the activation of MAPK and PI3K signaling cascades, but it is not clear whether IGF-1 activates mTOR, or operates in parallel to the PI3K-Akt-mTOR cascade through activation of MAPK



## Aims and Approach

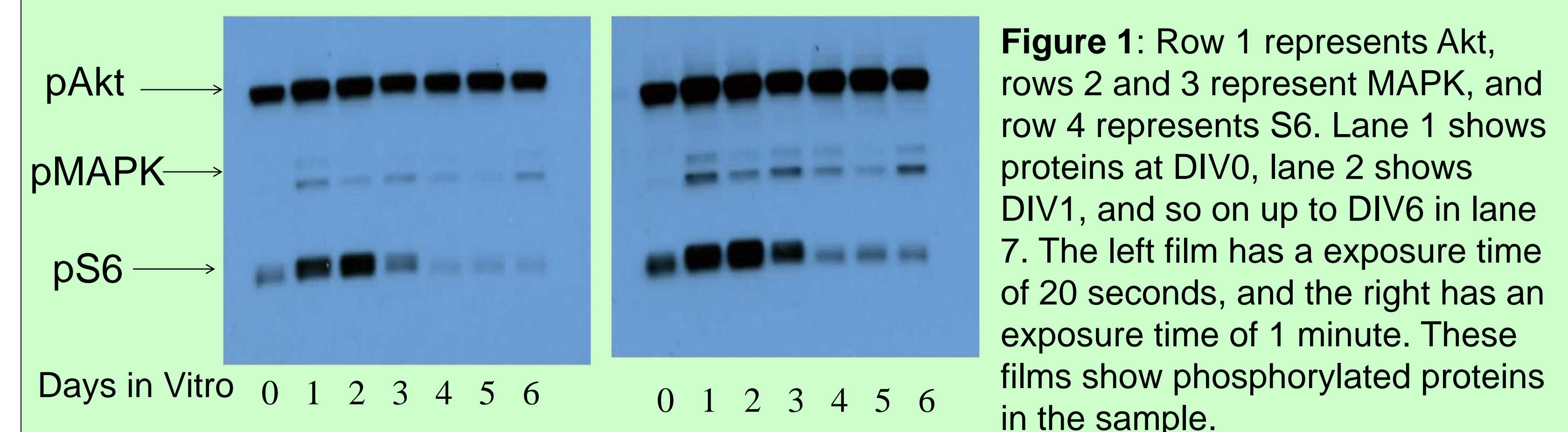
**Aim 1:** What are the downstream effectors of IGF-1 in an organotypic hippocampal culture model of posttraumatic epileptogenesis, and is there cross-talk with pro-epileptogenic PI3K-Akt-mTOR signaling?

In order to answer these questions, Western Blot is used to measure levels of phosphorylation of Akt, MAPK, and S6 (a marker of mTOR activation), during early post injury period and latent period with and without IGF-1 in the culture medium.

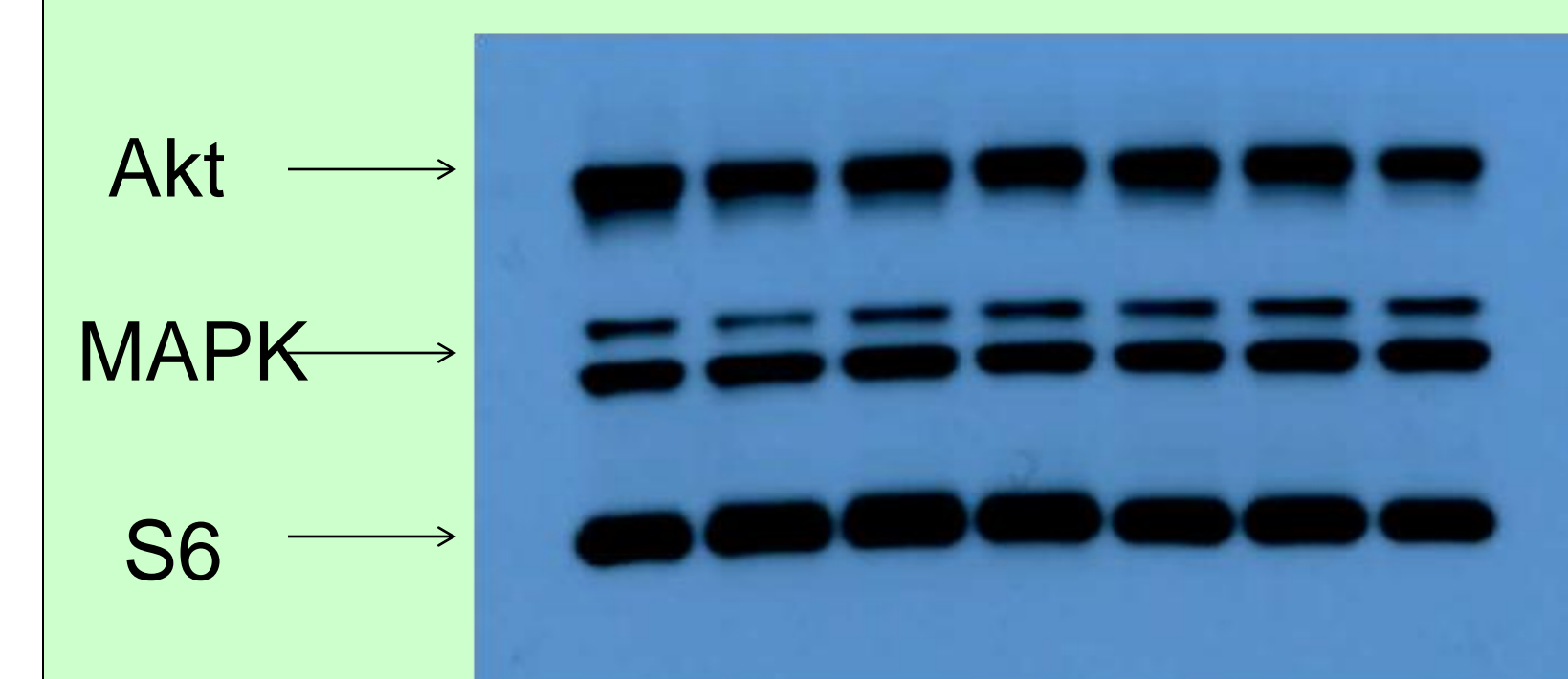
**Aim 2:** Determine the timeline of the signaling cascade.

Measuring the presence of phosphorylated Akt, MAPK, and S6 both with and without IGF-1 will lead to conclusions on the effects of IGF-1 on the different steps in the cascade. These conclusions will allow us to determine the sequence in which the pathway operates.

## Results

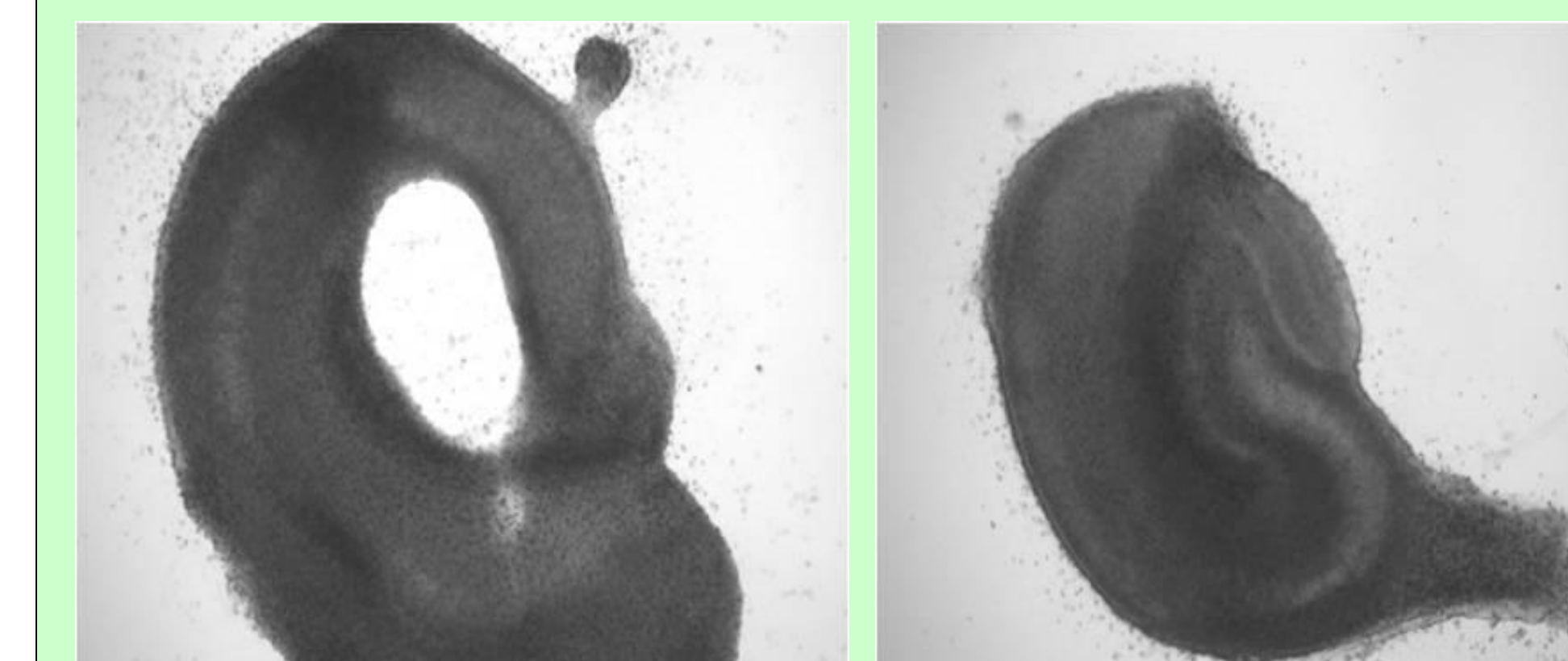


**Figure 1:** Row 1 represents Akt, rows 2 and 3 represent MAPK, and row 4 represents S6. Lane 1 shows proteins at DIV0, lane 2 shows DIV1, and so on up to DIV6 in lane 7. The left film has a exposure time of 20 seconds, and the right has an exposure time of 1 minute. These films show phosphorylated proteins in the sample.

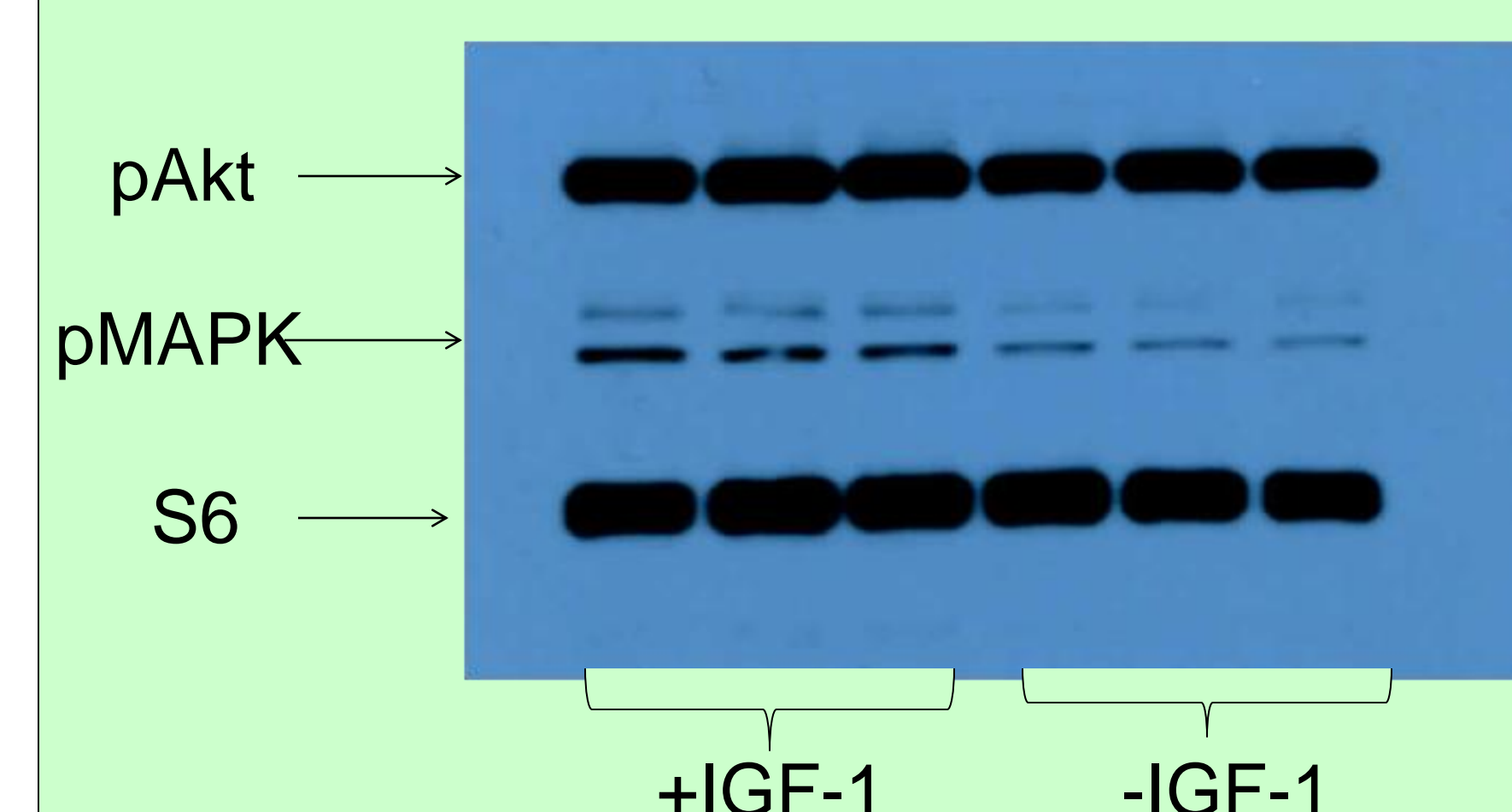


**Figure 2:** This image uses the same samples, but measures total Akt, S6, and MAPK rather than phosphorylated protein. Both are used so that a ratio can be made between phosphorylated and total protein in order to determine a relative phosphorylation.

In these films, it is clear that protein phosphorylation varies over time, with the greatest amounts of pS6 and pAkt occurring during DIV1 and DIV2. Although this does not prove any specific conclusion, it does show that during recovery, more activity occurs during the first and second day, and lessens as the days increase. These results give a basis for future experiments; samples should be tested at DIV3. This is when the circuits that were affected by the injury start to rebuild



**Figure 3:** The image on the left shows the slice from the first run of an experiment that was performed, while the figure on the right shows the repeated experiment. The hole in the left slice is damage, which led to negative results in this specific experiment. This shows the importance of the hippocampus slice.



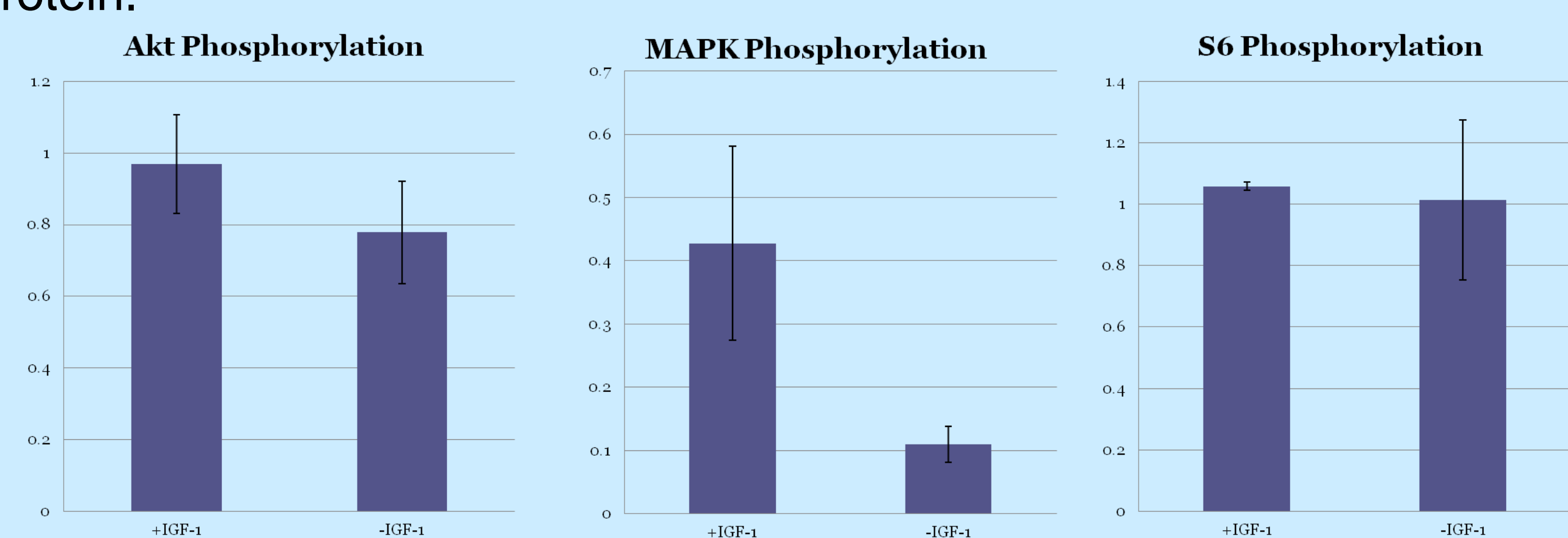
**Figure 4:** The film has an exposure time of 5 minutes. Lanes 1-3 were treated with +IGF-1 while lanes 4-6 were starved of IGF-1 at DIV3. The results of this experiment were positive for all three proteins. On this film, the +IGF-1 samples showed more protein phosphorylation than the -IGF-1 samples.

## Analysis

A program called Fiji ImageJ was used to collect the data for this experiment. This program gave values to each band based on band brightness, and these numerical values can be used to interpret the data and make relative ratios of phosphorylated protein to total protein.

$$\text{Activation} = \frac{\text{Phosphorylation}}{\text{Total Protein}}$$

**Figure 5:** These graphs show relative ratios of phosphorylated protein/total protein. From this data, we can conclude MAPK is the potential signaling effector in the pathway. This experiment does not finalize this fact, but a follow up study would be to inhibit MAPK to see how this affects epileptogenesis



## Conclusion

Over 30 experiments have been done, some being repeat experiments. So far, we have concluded that +IGF gives approximately 50% increase in phosphorylation of Akt and pS6. This is our only consistent conclusion to date, but it is clear that IGF-1 does have a positive effect on protein phosphorylation. MAPK also shows evidence of playing a role in the signaling cascade, but it is not clear how it effects the pathway. The question now is how exactly does IGF-1 respond to injury and what is the timeline of the cascade? This experiment is still in the workings, but once all data is collected and analyzed it will be possible to answer our first aim, make strides toward the second, and to continue on to accomplish the long term aim in the future.

## Acknowledgements

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